

REMARKS

Claims 31, 71, 76-82, 84, 85, 91-112, 115, and 121 were pending. Claims 31, 85, 92-95, 102-104, 110, and 121 have been amended to clarify the claimed invention. Specifically, claims 31, 92, 93, 102 and 121 have been amended to recite “an antibody specific for the alpha (2) macroglobulin receptor.” Support for this amendment is found in the specification, for example, at page 23, lines 6-18, and page 50, lines 1-2. Claim 93 has also been amended to clarify that the compound is an eptiope-binding fragment of a species of antibody recited in the claim. Claim 95 has been amended to clarify that the compound is an alpha (2) macroglobulin fragment. Support for this amendment is found in the specification, *e.g.*, at page 51, lines 11-22. Claim 101 has been amended to clarify that the compound is an alpha (2) macroglobulin receptor fragment. Support for this amendment is found in the specification, *e.g.*, at page 54, lines 7-16, and at page 13, lines 5-9 (description of Figure 3C). Claims 85, 92-95, and 110 have been amended to delete their dependency from a canceled claim. Claims 103 and 104 have been amended for clarity. Claims 71, 76-79, 84, 105, 106, 108, and 109 have been canceled without prejudice to Applicants’ right to pursue the subject matter thereof in a continuing application.

Claim Objections

The Examiner objected to claims 76 and 84 under 37 § C.F.R. 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of the previous claim. The Examiner stated that the term “antagonist” in claim 76 and the term “peptide” in claim 84 each read on a compound broader in scope than the compound of claims 31 or 71, from which claims 76 and 84 depend.

Applicants respectfully disagree and maintain that the terms “antagonist” and “peptide” are not of broader scope than the “compound” of claims 31 and 71. However, because Applicants believe that the claimed subject matter of claims 76 and 84 is unnecessary, and in order to expedite the prosecution of this application, claims 76 and 84 have been canceled. For example, claim 84 is deemed unnecessary in view of the antibody fragments specified in other dependent claims, *e.g.*, claims 92 and 93, and in view of the use of the term “peptide” in the specification to describe both peptides of at least 10 amino acids and longer protein fragments (see *e.g.*, page 51, lines 11-22).

Although the Examiner's rejection is moot in view of the cancellation of claims 76 and 84, Applicants nevertheless point out that the Examiner's rejection was based on an improper construction of the claims. Specifically, regarding claim 76, the Examiner used the description in the specification of the *kinds of compounds* which can be screened by the claimed methods, including both agonists and antagonists of various chemical structures, *e.g.*, small molecules, peptides, antibodies, etc., to construe the term "antagonist" in claim 76 as encompassing, *e.g.*, organic compounds (see pages 3 to 4 of the Office Action, citing to page 37, lines 8-14, of the specification). This is a plain error in claim construction, since the antagonist of claim 76 was limited by the claims from which it depended to a particular substance, namely an antibody, an $\alpha 2M$ receptor fragment, or an $\alpha 2M$ fragment. Thus, the antagonist of claim 76 could not properly have been construed to read on an "organic compound."

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 31, 71, 76, 77, 79-82, 84, 85, 91-107, 109-112, 115, and 121 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

Specifically, the Examiner acknowledges that the specification is enabling for the claimed method of inhibiting an immune response with an antibody specific for the $\alpha 2M$ receptor, but contends that the specification does not provide enablement for a compound which is "an antibody," "an $\alpha 2M$ receptor fragment," or "an $\alpha 2M$ fragment" according to the claims.

In response, Applicants note that claim 71 has been canceled. With respect to claim 31 and its dependent claims, the amendment of the claims renders this rejection moot with respect to a compound which is "an antibody" because the claims now specify that the antibody is specific for the $\alpha 2M$ receptor. With respect to a compound that is either an $\alpha 2M$ receptor fragment or an $\alpha 2M$ fragment, Applicants respectfully submit that the working examples and guidance provided by the specification, combined with the high degree of knowledge and skill in the art, enable the skilled person to use compounds having the

structure and function specified in the claims for inhibiting an immune response without undue experimentation, for the following reasons.

1. An α 2M receptor fragment which interferes with the interaction of a heat shock protein with the α 2M receptor

The specification provides a specific example of an α 2M receptor fragment, the p80 fragment, which binds to heat shock proteins. The specification at page 71-72 describes cross-linking and affinity purification experiments showing that gp96 binds to the p80 fragment of the α 2M receptor (see also the specification at 73, lines 13-19, identifying the p80 fragment as an amino terminal fragment of the α 2M receptor). The specification also demonstrates that the p80 fragment is involved in the interaction between heat shock proteins and the α 2M receptor which results in representation of heat shock protein-chaperoned antigenic peptide. See *e.g.*, the example at pages 72-73 of the specification showing that antibodies raised against the p80 fragment of the α 2M receptor inhibited representation of gp96-chaperoned antigenic peptides. Thus, the p80 fragment both binds to heat shock protein and is involved in the α 2M receptor immune activity. These results reasonably predict that the p80 fragment itself inhibits the interaction of heat shock protein with the α 2M receptor, *e.g.*, by binding to available heat shock protein, thereby preventing the interaction between the heat shock protein and the α 2M receptor. This is taught in the specification, *e.g.*, at page 50, lines 10-13, which provides that an antagonist may be a peptide comprising at least 10 contiguous amino acids of the α 2M receptor sequence which can bind to and “neutralize” an α 2M receptor ligand such as a heat shock protein.

Applicants submit that it was within the routine skill in the art to identify additional fragments of the α 2M receptor that interfere with the interaction between heat shock proteins and the α 2M receptor, using the guidance provided by the specification and further in view of the exemplary α 2M receptor fragments taught in the specification. See, *e.g.*, page 10 of Applicants’ June 9, 2005 Amendment, which discusses exemplary α 2M receptor fragments disclosed in the specification.

With respect to the amount of experimentation necessary to enable methods for inhibiting an immune response in a human using the claimed α 2M receptor fragments, Applicants maintain that the ability of a compound to inhibit a CTL response in an *in vitro* representation assay such as those described by the specific examples in the specification was

accepted in the art at the time of filing as reasonably predictive of the ability to inhibit an *in vivo* immune response (see section 3 below).

2. An α 2M fragment which interferes with the interaction of a heat shock protein with the α 2M receptor

The example at page 73, lines 20-28 of the specification demonstrates that α 2M, known in the art to be a ligand for the α 2M receptor, was able to inhibit representation of a gp96-chaperoned antigenic peptide. It follows that a fragment of α 2M which inhibits the interaction of a heat shock protein with the α 2M receptor would also inhibit representation of a heat shock protein-chaperoned antigenic peptide.

Applicants submit that it was within the routine skill in the art to identify fragments of α 2M that interfere with the interaction between heat shock proteins and the α 2M receptor, using the guidance provided by the specification and further in view of the exemplary α 2M fragments taught in the specification. See, *e.g.*, page 9 of Applicants' June 9, 2005 Amendment, which discusses the teachings in the specification of exemplary α 2M fragments.

With respect to the amount of experimentation necessary to enable methods for inhibiting an immune response in a human using the claimed α 2M fragments, Applicants maintain that the ability of a compound to inhibit a CTL response in an *in vitro* re-presentation assay such as those described by the specific examples in the specification was accepted in the art at the time of filing as reasonably predictive of the ability to inhibit an *in vivo* immune response (see section 3 below).

3. The *in vitro* assays described in the specification are reasonably predictive of the ability of a compound to inhibit an immune response *in vivo*.

In their Amendment mailed November 8, 2004, Applicants presented post-filing evidence to support their position that the ability of a compound to inhibit a CTL response in an *in vitro* representation assay such as those described by the specific examples in the specification was reasonably predictive of the ability of the compound to inhibit an immune response *in vivo* (see Binder and Srivastava, 2004). In their Amendment mailed June 9, 2005, Applicants presented evidence that the state of the art in 1995 demonstrated a correlation between the ability of heat shock protein-peptide complexes to stimulate cytotoxic T-lymphocytes ("CTL") in an *in vitro* representation assay and the ability to elicit a CTL response *in vivo* (see Suto and Srivastava, 1995, and Binder *et al.*, 2002). Accordingly,

Applicants maintain that the ability of a compound to modulate a CTL response in an *in vitro* representation assay was accepted in the art at the time of filing as reasonably predictive of the ability to modulate similarly an *in vivo* immune response. 35 U.S.C. § 112 requires no more. See *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996)(stating that the results of *in vitro* tests are sufficient to meet the written description requirement as long as they are reasonably correlated with a pharmacologically useful *in vivo* response).

In view of the results of the *in vitro* assays provided in the specification and the art-recognized correlation between such *in vitro* results and the ability to inhibit an immune response *in vivo*, Applicants maintain that one skilled in the art, following the teachings of the specification, would be able to identify and use an α 2M fragment, or an α 2M receptor fragment, that interferes with the interaction of a heat shock protein with the α 2M receptor and thereby inhibit an immune response according to the claimed methods.

In view of the foregoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

Claims 31, 76, 84, 92, 93, 102, 105, and 121 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleges that the specification fails to provide an adequate written description for a compound which is an "antibody" according to claims 31, 92, 93, 102, 105, and 121, or for a compound which is a "peptide" or "antagonist" according to claims 76 and 84, respectively.

Without conceding the correctness of the Examiner's rejection, Applicants note that claims 76, 84, and 105 have been canceled rendering the rejection moot with respect to those claims. Applicants submit that the amendment of claims 31, 92, 93, 102 and 121 to recite the antigen to which the claimed antibody binds, renders this rejection moot with respect to those claims.

In view of the foregoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, written description.

CONCLUSION

Applicants believe that the present claims meet all of the requirements for patentability. Entry and consideration of the foregoing remarks into the file of the subject application is respectfully requested.


If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

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